LIVER

Steatosis affects chronic hepatitis C progression in a genotype specific way

L Rubbia-Brandt, P Fabris, S Paganin, G Leandro, P-J Male, E Giostra, A Carlotto, L Bozzola, A Smedile, F Negro

See end of article for authors' affiliations
....

Correspondence to:
Dr F Negro, Divisions of Gastroenterology and Hepatology and of Clinical Pathology, Hôpital Cantonal Universitaire, 24 rue Micheli-du-Crest, CH-1211 Genève 14, Switzerland;
Francesco.Negro@dim.hcuge.ch

Background and aims: Liver steatosis is frequent in chronic hepatitis C, particularly in patients infected with hepatitis C virus (HCV) genotype 3. The aim of this study was to determine the relationship between steatosis and fibrosis in chronic hepatitis C as a function of viral genotype.

Methods: A multivariable logistic regression analysis was carried out in 755 chronic hepatitis C patients (mean body mass index (BMI) 24.11 kg/m^2; 178 with genotype 3), consecutively admitted to three referral hospitals. Liver histology showed steatosis in 315 and fibrosis in 605 patients, of whom 187 had cirrhosis (78 compensated and 109 decompensated).

Results: Steatosis was independently associated with fibrosis (p<0.001), genotype 3 (p<0.001), BMI (p<0.001), ongoing alcohol abuse (p<0.001), and age (p=0.001). Fibrosis was associated with the Metavir activity score (p<0.001), age (p<0.001), steatosis (p=0.001), past alcohol abuse for >5 years (p=0.015), and BMI (p=0.034). When regression analysis was repeated on patients divided according to viral genotype (that is, 3 v non-3) to identify type specific risk factors, steatosis was associated with ongoing alcohol abuse (p<0.001) and age (p=0.01) only in non-3 genotype infected patients and with Metavir activity (p=0.044) only in genotype 3 infected patients. Similarly, fibrosis was associated with steatosis only in genotype 3 infected individuals (p=0.018), and with past alcohol abuse (p=0.003) and (marginally) diabetes (p=0.078) only in non-3 genotype infected patients.

Conclusions: Steatosis influences chronic hepatitis C progression in a genotype specific way. Patients infected with genotype 3 and histologically confirmed steatosis should not be deferred from effective antiviral therapy.

C hronic infection with the hepatitis C virus (HCV) is a major cause of progressive liver damage and the long term sequelae include cirrhosis and primary hepatocellular carcinoma.[1] Although most HCV associated liver damage is immunomediated,[2] some histopathological features, such as liver steatosis, suggest a viral cytopathic effect.[3 4]

Several observations indicate that steatosis may be directly due to HCV: its association with genotype 3,[3 5–9] correlation between its severity and level of HCV replication,[3 7] and its disappearance on response to antiviral therapy.[3 9 10] However, some data suggest that the pathogenesis of mild steatosis of most HCV infected patients may be metabolic as its severity correlates with body mass index (BMI)[7] whereas only the moderate to severe steatosis typically found in patients with genotype 3 may be HCV related.[3 7] Thus steatosis observed in chronic hepatitis C is not always virally related as other factors may coexist. This is not surprising considering the frequency of liver steatosis in the general population (~15%).[11 12]

A major question concerns the impact of steatosis on liver disease progression, as suggested by some authors.[3 6–8 13] Cohort studies on patients with non-alcoholic fatty liver disease show that simple steatosis runs a benign non-progressive clinical course.[14 15] However, steatosis in chronic hepatitis C is almost invariably accompanied by some degree of necroinflammation. Thus steatosis may contribute to liver disease progression either directly or via a synergistic effect with inflammation or other cofactors. To address this issue, we analysed the role of HCV and other factors of liver steatosis and fibrosis in 755 chronic hepatitis C patients by multivariable logistic regression. We then repeated the analysis after stratifying patients according to HCV genotype—that is, patients infected with genotype 3 (in whom steatosis is mostly caused by HCV) versus those with other genotypes, in whom other causes of steatosis and, possibly, liver fibrosis progression, may prevail.

PATIENTS AND METHODS

Study population

A total of 755 chronic hepatitis C patients were sequentially collected at three centres (303 from Geneva, Switzerland, 198 from Torino, Italy, and 254 from Vicenza, Italy). Inclusion criteria included: (1) a liver biopsy performed for diagnostic purposes showing chronic hepatitis; (2) detectable HCV RNA in serum; and (3) a HCV genotype belonging to genotypes 1–4. Patients with infection with HCV genotypes 5 or 6, active liver disease related to hepatitis B virus, infection with the human immunodeficiency virus 1, stigmata of autoimmune liver disease (as defined by international criteria),[16] or drug induced liver damage were excluded from the study.

This study was conducted in conformity with the Helsinki declaration and all patients consented to participate.

Statistical procedure

All patients fulfilling the above criteria were studied to assess the relationship between steatosis and fibrosis by means of both univariate and multivariate stepwise logistic regression analyses. For both analyses, when steatosis was used as the dependent variable (that is, absence v presence of steatosis,

....

Abbreviations: HCV, hepatitis C virus; BMI, body mass index; OR, odds ratio

independent of its severity), we considered the following as independent variables: sex, age, HCV genotype, ongoing alcohol abuse (>40 g/day, based on self reporting), BMI (kg body weight/(body height in meters)[2]), history of diabetes, liver disease activity score (Metavir),[17] and a modified fibrosis score. For the latter, we took into account the Metavir fibrosis score and the clinical stage of disease in order to divide patients into four separate groups: those without fibrosis, those with portal fibrosis without septa or with a few septa (Metavir F1-2), those with extensive fibrosis (Metavir F3-F4) but compensated liver disease, and finally those with decompensated cirrhosis, included at the time of liver transplant. When fibrosis was used as the dependent variable (that is, absent or present, irrespectively of the score), we considered the following as independent variables: sex, age, HCV genotype, past alcohol abuse (>40 g/day for >5 years), BMI, history of diabetes, Metavir activity score,[17] and severity of steatosis. The latter was graded as 0 or absent (<1% of total hepatocytes), 1 or mild (between 1% and 30% of hepatocytes), 2 or moderate (between 30% and 60% of hepatocytes), and 3 or severe (>60% of hepatocytes).[18] As liver biopsies were evaluated at three centres, in order to minimise the impact of interobserver variability we randomly selected 10% of histological slides at the two centres of Torino and Vicenza and these were read by the Geneva pathologist (LR-B) who had already evaluated the largest number of cases. The rate of concordance with the original scores was 95%.

Univariate analysis was performed by the χ^2 test for frequencies and by the Mann-Whitney rank sum test for means. Stepwise logistic regression was used to evaluate the independent association of the considered variables with steatosis and fibrosis, taking into consideration the possible centre effect. The maximum likelihood method was used for entering or removing variables at each step. Bio Medical Data Processing (BMDP, Dynamic version 7.0, Los Angeles, California, USA) was used for calculations.

RESULTS
Patient features
Tables 1 and 2 report the baseline characteristics of the 755 chronic hepatitis C patients: 315 (41.7%) had steatosis and 187 (24.8%) cirrhosis. Among these, 109 were included at the time of liver transplant.

Table 1 Characteristics of the 755 patients considered in the logistic regression analyses

Sex (%)	
Male	533 (70.6)
Female	222 (29.4)
Age (mean (SD))	43.37 (12.01)
HCV genotype (%)	
1	401 (53.1)
2	121 (16.0)
3	178 (23.6)
4	55 (7.3)
BMI (mean (SD))	24.11 (3.21)
Ongoing alcohol abuse (%)	84 (11.1)
Past alcohol abuse (%)	164 (21.7)
History of diabetes (%)	43 (5.7)
Metavir activity score (%)	
A0	181 (24.0)
A1	367 (48.6)
A2	164 (21.7)
A3	43 (5.7)
Fibrosis score (%)	
F0	157 (20.8)
F1–F2	350 (46.4)
F3–F4, compensated	78 (10.3)
F4, decompensated	109 (14.4)
Steatosis score (%)	
0	440 (58.3)
1	206 (27.3)
2	69 (9.1)
3	40 (5.3)

BMI, body mass index.

Table 2 reports patient features divided into two groups—that is, patients infected with HCV genotype 3 versus those infected with other genotypes. Patients with genotype 3 were younger (p<0.001), had a lower BMI (p<0.001), had less frequently a history of diabetes (p = 0.014), had more frequently a moderate or severe steatosis (p<0.001) or a fibrosis score of F1-F2, and were less likely to present with decompensated liver disease.

Univariate analysis
Tables 3 and 4 report the results of the univariate analysis using, respectively, steatosis and fibrosis as the dependent variables. Patients with liver steatosis were more likely to be older (p = 0.002) and have a higher BMI (p<0.001). Liver

Table 2 Characteristics of the 755 patients considered in the logistic regression analyses divided according to hepatitis C virus (HCV) genotype

	All genotype 3 (n = 178)	All non-3 genotypes (n = 577)	p Value
Male sex (%)	133 (74.7)	400 (69.3)	NS
Age (mean (SD))	37.2 (8.7)	45.3 (12.3)	<0.001
BMI (mean (SD))	22.9 (2.7)	24.5 (3.3)	<0.001
Ongoing alcohol abuse (%)	24 (13.5)	60 (10.4)	NS
Past alcohol abuse (%)	45 (25.3)	119 (20.6)	NS
History of diabetes (%)	3 (1.7)	40 (6.9)	0.014
Metavir activity score (%)			
A0	51 (28.7)	130 (22.5)	
A1	75 (42.1)	292 (50.6)	NS
A2	39 (21.9)	125 (21.7)	
A3	13 (7.3)	30 (5.2)	
Fibrosis score (%)			
F0	38 (21.3)	119 (19.1)	
F1–F2	101 (56.7)	249 (43.2)	<0.001
F3–F4, compensated	30 (16.9)	109 (18.9)	
F4, decompensated	9 (5.1)	100 (17.3)	
Steatosis score (%)			
0	69 (38.8)	371 (64.3)	
1	51 (28.7)	155 (26.9)	<0.001
2	27 (15.2)	42 (7.3)	
3	31 (17.4)	9 (1.6)	

BMI, body mass index.

Table 3 Univariate analysis of factors associated with liver steatosis in 755 chronic hepatitis C patients

	Steatosis		
Variable	No (n = 440)	Yes (n = 315)	p Value
Male sex (%)	300 (68.2)	233 (74)	0.10
Age (mean (SD))	42.2 (12.4)	45.0 (11.3)	0.002
HCV genotype (%)			
1	258 (58.6)	143 (45.4)	
2	80 (18.2)	41 (13)	<0.001
3	69 (15.7)	109 (34.6)	
4	33 (7.5)	22 (7)	
Ongoing alcohol abuse (%)	24 (5.5)	60 (19)	<0.001
BMI (mean (SD))	23.7 (3.1)	24.7 (3.2)	<0.001
History of diabetes (%)	21 (4.8)	22 (7)	0.257
Metavir activity score (%)			
A0	116 (26.4)	65 (20.6)	
A1	223 (50.7)	144 (45.7)	0.011
A2	82 (18.6)	82 (26)	
A3	19 (4.3)	24 (7.6)	
Fibrosis score (%)			
F0	116 (26.4)	41 (13)	
F1–F2	200 (45.4)	150 (47.6)	<0.001
F3–F4, compensated	50 (11.4)	89 (28.2)	
F4, decompensated	74 (16.8)	35 (11.1)	

HCV, hepatitis C virus; BMI, body mass index.

steatosis was also associated with liver fibrosis (p<0.001), HCV genotype (p<0.001), ongoing alcohol abuse (p<0.001), and Metavir activity score (p = 0.011).

Similarly, fibrosis was associated with age (p<0.001), Metavir activity score (p<0.001), steatosis score (p<0.001), and past alcohol abuse (p = 0.006). BMI and history of diabetes approached (without reaching) statistical significance (p = 0.096 and p = 0.086, respectively).

Steatosis scores were significantly associated with the stage of liver disease, according to our modified scores (p<0.001) (fig 1). When all patients were considered (fig 1A), the majority of patients without fibrosis had no steatosis (116/ 157 (73.9%)). When the fibrosis score increased to F1–F2, there were still 200/350 (57.1%) patients who lacked steatosis but the proportion of patients with steatosis scores 2 (n = 35) to 3 (n = 22) increased to 16.3%. This increase was more

significant in patients with a fibrosis score of F3–F4 (with compensated liver disease) as moderate (n = 20) to severe (n = 12) steatosis was found in 23% of cases. In patients with decompensated cirrhosis however, most (74/109 or 67.9%) lacked steatosis, and moderate to severe steatosis was rare (5/ 109 (4.6%)). Similar variations were seen when patients were stratified according to genotype (fig 1B–C).

Multivariate analysis on all patients
Tables 5 and 6 show the results of multivariable logistic regression analysis performed on all 755 patients. Steatosis was associated with fibrosis score (p<0.001), HCV genotype (p<0.001), BMI (p<0.001), ongoing alcohol abuse (p<0.001), and age (p = 0.001) (table 5). The strongest association was with genotype 3 and, for fibrosis, the association increased with progression of the fibrosis score.

Table 4 Univariate analysis of factors associated with liver fibrosis in 755 chronic hepatitis C patients

	Fibrosis		
Variable	No (n = 157)	Yes (n = 598)	p Value
Male sex (%)	109 (69.4)	424 (70.9)	0.793
Age (mean (SD))	37.3 (11.2)	45.0 (11.7)	<0.001
HCV genotype (%)			
1	73 (46.5)	328 (54.8)	
2	29 (18.5)	92 (15.4)	0.159
3	38 (24.2)	140 (23.4)	
4	17 (10.8)	38 (6.3)	
Past alcohol abuse (%)	21 (13.4)	143 (23.9)	0.006
BMI (mean (SD))	23.7 (3.3)	24.2 (3.2)	0.096
History of diabetes (%)	4 (2.5)	39 (6.5)	0.086
Metavir activity score (%)			
A0	72 (45.9)	109 (18.2)	
A1	63 (40.1)	304 (50.8)	<0.001
A2	18 (11.5)	146 (24.4)	
A3	4 (2.5)	39 (6.5)	
Steatosis score (%)			
0	116 (73.9)	324 (54.2)	
1	26 (16.6)	180 (30.1)	<0.001
2	11 (7)	58 (9.7)	
3	4 (2.5)	36 (6)	

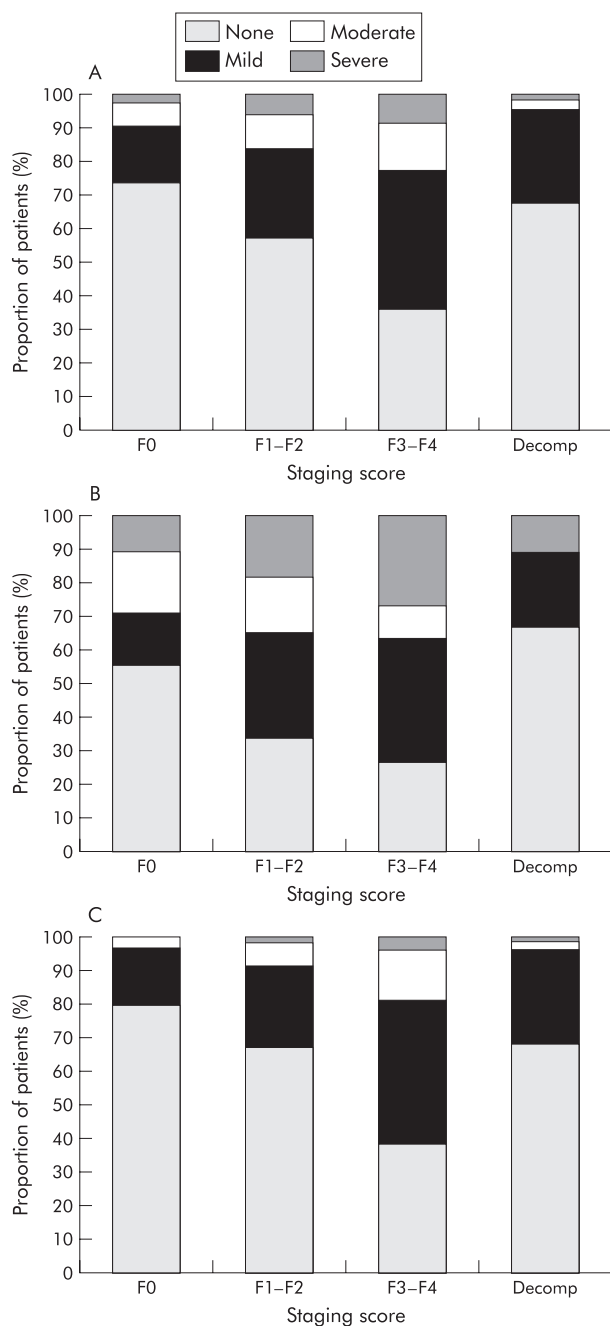HCV, hepatitis C virus; BMI, body mass index.

Figure 1 Proportion of chronic hepatitis C patients with or without steatosis according to stage of liver disease (for details on the scoring system of the liver disease stage, see methods section). (A) All 755 patients. (B) Only the 178 patients infected with the hepatitis C virus (HCV) genotype 3. (C) All 577 patients infected with HCV non-3 genotypes. Decomp, decompensated.

In fact, assuming an odds ratio (OR) of 1 for the absence of fibrosis, OR was 1.79 for scores F1–F2 and 2.95 for scores F3–F4 with compensated liver disease. In patients with decompensated cirrhosis, OR decreased to 0.93 but the negative association was not statistically significant (table 5).

When liver fibrosis was considered as the dependent variable, its presence was associated with Metavir activity score (p<0.001), age (p<0.001), steatosis score (p = 0.001), past alcohol abuse (p = 0.015), and BMI (p = 0.034) (table 6). The significance of the association with fibrosis, for both Metavir activity and steatosis, increased in parallel with their score values (table 6).

Multivariate analysis on patients with HCV genotype 3

When we considered the 178 patients with HCV genotype 3, the presence of steatosis was associated with fibrosis score (p = 0.011), BMI (P = 0.035), and Metavir activity score (p = 0.044) (table 7). As far as the association with fibrosis is concerned, it increased in parallel with the increase in fibrosis score. Assuming OR = 1 for the absence of fibrosis, the OR was 3.16 for scores F1–F2, and 5.10 for scores F3–F4 and compensated liver disease. In patients with decompensated cirrhosis however, the OR decreased to 0.308 (although the negative association was statistically not significant) (table 7). Regarding the Metavir activity score, although the relationship was significant when all patients were considered together, the statistical association lost significance when the population was divided according to individual scores.

When we considered (table 8) fibrosis as the dependent variable, it was found to be associated with Metavir activity score (p<0.001), age (p = 0.005), and steatosis score (p = 0.018). In particular, the significance of the association with Metavir activity increased in parallel with its scores. For steatosis, the OR was significant only for mild steatosis (table 8).

Multivariate analysis on patients infected with a HCV genotype other than 3

Finally, we considered only patients (n = 577) infected with a HCV genotype other than 3. When steatosis was the dependent variable (table 9), it was associated with ongoing alcohol abuse (p<0.001), BMI (p<0.001), fibrosis score (p<0.001), and age (p = 0.010) (table 9).

We then considered fibrosis as the dependent variable (table 10) we found it was associated with Metavir activity score (p<0.001), age (p<0.001), and past alcohol abuse (p = 0.003). A history of diabetes approached statistical significance (p = 0.078).

DISCUSSION

We have demonstrated, using a large multivariable logistic regression analysis stratified according to HCV genotype, that liver steatosis is associated with liver fibrosis only in chronic hepatitis C patients infected with genotype 3. In patients infected with other genotypes, age, prolonged alcohol abuse and possibly history of diabetes may prevail in determining the progression of liver disease.

These findings add to other analyses (mostly univariate[6 7 13 19] and in two cases multivariate[8 20]) published previously. There are some noteworthy differences as to their conclusions, partly due to discrepancies in scoring histological parameters or clinical variables such as alcohol abuse, but mostly due to major differences in patient baseline features. In a multivariable logistic regression from the USA,[8] the only independent predictors of steatosis were BMI and genotype 3. However, excluding 17 patients with risk factors for non-alcoholic steatohepatitis, only genotype remained as a factor affecting steatosis. Moreover, steatosis and liver inflammation were the only independent predictors of liver fibrosis, thus excluding a likely role of a history of alcohol abuse. We partially confirmed these results but we also identified fibrosis score, ongoing alcohol abuse, and age as further independent predictors of steatosis, and age and past alcohol abuse as further predictors of fibrosis. These discrepancies may be due to different population features—that is, the relative proportion of patients with viral versus non-viral steatosis. Studies carried out in the USA[8] and Australia[13] were characterised by a higher BMI and a lower percentage of patients with genotype 3 whereas European patients had a lower BMI (<25 in all four studies)[6 7 19 20] and were more frequently infected with genotype 3.

Table 5 Multivariable logistic regression analysis of factors associated with liver steatosis in 755 chronic hepatitis C patients

Variable	OR	95% CI	p Value
Fibrosis score*			
F1-F2	1.79	1.12–2.85	
F3-F4, compensated	2.95	1.67–5.24	<0.001
F4, decompensated	0.93	0.494–1.75	
HCV genotype*			
2	1.11	0.673–1.82	
3	4.89	3.09–7.72	<0.001
4	1.41	0.711–2.81	
BMI	1.11	1.05–1.17	<0.001
Ongoing alcohol abuse	3.59	2.04–6.32	<0.001
Age	1.03	1.01–1.05	0.001

*Odds ratio (OR) = 1 for a fibrosis score of F0 and HCV genotype 1.
HCV, hepatitis C virus; BMI, body mass index.

Table 6 Multivariable logistic regression analysis of factors associated with liver fibrosis in 755 chronic hepatitis C patients

Variable	OR	95% CI	p Value
Metavir activity score*			
A1	7.91	4.45–14.0	
A2	13.7	6.67–28.3	<0.001
A3	14.3	4.45–46.0	
Age	1.05	1.00–1.09	<0.001
Steatosis score*			
1	2.14	1.22–3.77	
2	2.39	1.06–5.36	0.001
3	3.87	1.27–11.8	
Past alcohol abuse	2.02	1.12–3.63	0.015
BMI	0.928	0.866–0.995	0.034

*Odds ratio (OR) = 1 for a Metavir activity score of A0 and a steatosis score of 0.
BMI, body mass index.

Table 7 Multivariable logistic regression analysis of factors associated with liver steatosis in 178 chronic hepatitis C patients infected with the hepatitis C virus (HCV) genotype 3

Variable	OR	95% CI	p Value
Fibrosis score*			
F1–F2	3.16	1.27–7.82	
F3–F4, compensated	5.10	1.44–18.1	0.011
F4, decompensated	0.308	0.0523–1.81	
BMI	1.17	1.02–1.34	0.035
Metavir activity score*			
A1	0.570	0.226–1.44	
A2	1.74	0.531–5.67	0.044
A3	0.235	0.0518–1.06	

*Odds ratio (OR) = 1 for a fibrosis score of F0 and a Metavir activity score of A0.
BMI, body mass index.

Table 8 Multivariable logistic regression analysis of factors associated with liver fibrosis in 178 chronic hepatitis C patients infected with the hepatitis C virus (HCV) genotype 3

Variable	OR	95% CI	p Value
Metavir activity score*			
A1	31.9	7.36–138	
A2	47.8	8.23–278	<0.001
A3	70.0	5.74–8.52	
Age	1.09	1.02–1.17	0.005
Steatosis score*			
1	7.44	1.76–31.44	
2	2.74	0.674–11.1	0.018
3	3.90	0.957–15.9	

*Odds ratio (OR) = 1 for a Metavir activity score of A0 and a steatosis score of 0.

Table 9 Multivariable logistic regression analysis of factors associated with liver steatosis in 577 chronic hepatitis C patients infected with hepatitis C virus (HCV) genotypes other than 3

Variable	OR	95% CI	p Value
Ongoing alcohol abuse	4.91	2.57–9.38	<0.001
BMI	1.11	1.04–1.18	<0.001
Fibrosis score*			
F1–F2	1.52	0.861–2.69	
F3–F4, compensated	3.16	1.63–6.13	<0.001
F4, decompensated	1.09	0.536–2.20	
Age	1.03	1.01–1.05	0.010

*Odds ratio (OR) = 1 for a fibrosis score of F0.
BMI, body mass index.

Table 10 Multivariable logistic regression analysis of factors associated with liver fibrosis in 577 chronic hepatitis C patients infected with hepatitis C virus (HCV) genotypes other than 3

Variable	OR	95% CI	p Value
Metavir activity score*			
A1	5.62	2.94–10.7	
A2	10.8	4.74–24.5	<0.001
A3	10.2	2.63–39.4	
Age	1.05	1.02–1.07	<0.001
Past alcohol abuse	2.65	1.34–5.23	0.003
History of diabetes	2.77	0.787–9.75	0.078

*Odds ratio (OR) = 1 for a Metavir activity score of A0.

Our most significant finding was that the role of steatosis in affecting liver fibrosis seems to be limited to patients with genotype 3, in agreement with another recent small univariate analysis from Sweden.[19] This is possibly due to the lower BMI of our patients compared with both American and Australian studies.[8][13] This finding is even more significant if we consider that patients infected with genotype 3 were younger (and possibly had a shorter duration of disease) and had a lower BMI compared with patients with other genotypes. The shorter duration of disease in patients with genotype 3 is also indirectly proven by the fewer patients with decompensated liver disease at enrolment. In patients infected with non-3 genotypes, age and history of alcohol abuse were major determinants of fibrosis (apart from liver inflammation), with diabetes following closely behind. The mechanism linking steatosis and fibrosis in patients with genotype 3 is unclear. Interestingly, among these patients (at variance with those infected with non-3 genotypes), steatosis was associated with Metavir activity, suggesting that it may be a cofactor contributing to inflammation (and hence to fibrogenesis). The opposite situation—that is, that liver inflammation is the origin of steatosis—seems unlikely because there was no association between inflammation and steatosis in patients with comparable levels of liver disease activity and non-3 genotypes.

The relationship between steatosis and fibrosis deserves further comment in view of the peculiar scoring system we adopted to classify fibrosis stages. The 109 patients with decompensated cirrhosis recruited at the time of liver transplantation, albeit presenting with a Metavir score of F4,[17] were considered as belonging to a more advanced phase of liver disease and given a distinct score. Also, the remaining classes of fibrosis were reclassified, and patients with Metavir scores of F1–F2 on the one hand, and F3–F4 scores on the other, were grouped together. This scoring system allowed us to observe an interesting phenomenon, consistent with our previous observations.[20] The odds of having liver steatosis increased with progression of liver fibrosis, independent of viral genotype. However, when liver disease progressed to decompensation, the risk of having any degree of liver steatosis fell sharply to 4.6%, independent of viral genotype, suggesting that in late stages of hepatitis C steatosis disappears, independent of its cause, as is the case for other liver diseases.[21–23] Whether this depends on reduced calorie intake, systemic shunting of portal blood, or sinusoidal capillarisation remains unclear.[23]

In conclusion, we have shown that in chronic hepatitis C, steatosis may influence liver fibrosis progression in a genotype specific way. In patients with genotype 3, the presence of steatosis, which is due to HCV replication and is frequently moderate to severe, correlates with the liver fibrosis score. In contrast, steatosis and fibrosis are not associated in patients with HCV genotypes other than 3, in whom steatosis is milder and unrelated to HCV replication. In these patients, progression of liver disease may depend on other factors, such as prolonged alcohol abuse or being overweight. These results have practical implications for patient clinical management. Patients infected with HCV genotype 3 and presenting with liver steatosis, especially if moderate to severe, should be offered antiviral therapy, irrespective of other considerations, especially knowing that the rate of success in this setting, with currently available regimens, is very high.[24] Measures aimed at reducing the risk of liver disease progression in patients with genotypes other than 3, in addition to antiviral treatment, should also include strict abstinence from alcohol and body weight control.

ACKNOWLEDGEMENTS

....
Authors' affiliations

L Rubbia-Brandt*, Division of Clinical Pathology, Hôpitaux Universitaires, Genève, Switzerland

P Fabris*, Division of Infectious Diseases, Ospedale S Bortolo, Vicenza, Italy

S Paganin, P-J Male, E Giostra, Division of Gastroenterology and Hepatology, Hôpitaux Universitaires, Genève, Switzerland

G Leandro, Division of Gastroenterology, Ospedale Saverio de Bellis, Castellana Grotte, Italy

A Carlotto, Division of Infectious Diseases, Ospedale Camillo de Lellis, Schio, Italy

L Bozzola, Division of Pathology, Ospedale S Bortolo, Vicenza, Italy

A Smedile, Department of Gastroenterology, Ospedale S Giovanni Battista, Torino, Italy

F Negro, Division of Clinical Pathology, and Division of Gastroenterology and Hepatology, Hôpitaux Universitaires, Genève, Switzerland

*Drs Rubbia-Brandt and Fabris contributed equally to this work.

REFERENCES

1 **National Institutes of Health Consensus Development Conference**. Management of Hepatitis C: 2002. *Hepatology* 2002;**36**(suppl 1):S1–252.
2 **Rehermann B**. Interaction between the hepatitis C virus and the immune system. *Semin Liver Dis* 2000;**20**:127–41.
3 **Rubbia-Brandt L**, Quadri R, Abid K, *et al*. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol* 2000;**33**:106–15.
4 **Goodman ZD**, Ishak KG. Histopathology of hepatitis C virus infection. *Semin Liver Dis* 1995;**15**:70–81.
5 **Mihm S**, Fayyazi A, Hartmann H, *et al*. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology* 1997;**25**:735–9.
6 **Serfaty L**, Andreani T, Giral P, *et al*. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001;**34**:428–34.
7 **Adinolfi LE**, Gambardella M, Andreana A, *et al*. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001;**33**:1358–64.
8 **Monto A**, Alonzo J, Watson JJ, *et al*. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol. *Hepatology* 2002;**36**:729–36.
9 **Kumar D**, Farrell GC, Fung C, *et al*. Hepatitis C virus genotype 3 is cytopathic to hepatocytes. Genotype-specific reversal of hepatic steatosis after sustained response to antiviral therapy. *Hepatology* 2002;**36**:1266–72.
10 **Rubbia-Brandt L**, Giostra E, Mentha G, *et al*. Expression of liver steatosis in hepatitis C virus infection and pattern of response to alpha-interferon. *J Hepatol* 2001;**35**:307.
11 **Nomura H**, Kashiwagi S, Hayashi J, *et al*. Prevalence of fatty liver in a general population of Okinawa, Japan. *Jpn J Med* 1988;**27**:142–9.
12 **Bellentani S**, Tiribelli C. The spectrum of liver disease in the general population: lessons from the Dionysos study. *J Hepatol* 2001;**35**:531–7.
13 **Hourigan LF**, Macdonald GA, Purdie D, *et al*. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999;**29**:1215–19.
14 **Teli MR**, James OF, Burt AD, *et al*. The natural history of nonalcoholic fatty liver: a follow-up study. *Hepatology* 1995;**22**:1714–19.
15 **Matteoni CA**, Younossi ZM, Gramlich T, *et al*. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;**116**:1413–19.
16 **McFarlane IG**. Autoimmune hepatitis: diagnostic criteria, subclassifications, and clinical features. *Clin Liver Dis* 2002;**6**:317–33.
17 **Bedossa P**, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996;**24**:289–93.
18 **D'Alessandro AM**, Kalayoglu M, Sollinger HW, *et al*. The predictive value of donor liver biopsies for the development of primary non-function after orthotopic liver transplantation. *Transplantation* 1991;**51**:157–63.
19 **Westin J**, Nordlinder H, Lagging M, *et al*. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002;**37**:837–42.
20 **Rubbia-Brandt L**, Leandro G, Spahr L, *et al*. Liver steatosis in chronic hepatitis C: a morphological sign suggesting infection with HCV genotype 3. *Histopathology* 2001;**39**:1–6.
21 **Powell EE**, Cooksley WG, Hanson R, *et al*. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology* 1990;**11**:74–80.
22 **Abdelmalek M**, Ludwig J, Lindor KD. Two cases from the spectrum of nonalcoholic steatohepatitis. *J Clin Gastroenterol* 1995;**20**:127–30.
23 **Poonawala A**, Nair SP, Thuluvath PJ. Prevalence of obesity and diabetes in patients with cryptogenic cirrhosis: a case-control study. *Hepatology* 2000;**32**:689–92.
24 **Fried M**, Shiffman ML, Reddy KR, *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus. *N Engl J Med* 2002;**347**:975–82.